EXHIBIT A - PAGE 1

ARTHRITIS FOUNDATION RESEARCH GRANTS

Type of Applicati n: *(check one)*

- ☐ Biomedical Science Grant
- ☑ Clinical Science Grant
- ☐ New Investigator Grant

Study Section: *(check one)*

- ☐ Behavioral/Epidemiology
- ☐ Biochemistry
- ☐ Cell Biology
- ☐ Cellular Immunology
- ☐ Clinical Immunology
- ☐ Inflammation
- ☐ Molecular Biology
- ☐ Molecular Immunology
- ☑ Technologies/Biomechanics

1. Full Name of Principal Investigator:
Timothy E. McAlindon

2. Degree *(type, date, field)*:
BM 1982 Medicine; DM 1993 Medicine, MPH 1995 Epi/Biostat

3. Position Title:
Assistant Professor of Medicine

4. Social Security Number:
017-78-1444

5. Applicant's Mailing Address:
Boston University Medical Campus
715 Albany Street, A203
Boston, MA 02118

6. Supervisor/Mentor *(if applicable)*:

7. Office Phone: 617-638-5453
Fax Number 617-638-5239
E-mail Address tmcalind@bu.edu

8. Dates of Entire Proposed Project:
7 / 01 / 99 through 6 / 30 / 2002

9. Title of Research Project:
A Study Of The Feasibility Of Internet-Based Clinical Trials In Osteoarthritis

10. Citizenship: U.S. ☐ or Other ☑. If "Other", state name of country: United Kingdom, #747 192261
Do you have a permanent visa? Yes ☑ or No ☐. If "Yes", state number:

11. Have you previously applied for support from the Arthritis Foundation? Yes ☑ or No ☐.
If "Yes", state year and type of application. Was it funded? Yes ☐ or No ☒.

12. Official in Grants and Contracts Office to be notified if an award is made *(name, title, address, phone)*.

Barbara A. Cole
Executive Director of Financial Affairs
Boston University Medical Campus
715 Albany Street - 560
Boston, MA 02118
Phone: 617-638-4590, Fax 617-638-5449, email: barbcole@bu.edu

13. By signing below, applicant agrees to permit his or her name, application title, abstract, critique and score to be shared with local chapters wishing to consider a successful applicant for funding.

E McAlind — 7/31/98

Signature of Principal Investigator — Date

Form 2 R4/98

EXHIBIT A - PAGE 2

14. ABSTRACT Principal Investigator's Last Name: McAlindon, Timothy

(Please underline 5 key words)

The explosive gr wth in Internet use during the last few years has made it possible to communicate with great numbers of people on-line than with any other technology. Recent software advances have made it possible to transmit and collect secure data from remote individuals over the Internet in an efficient and interactive manner. Thus, the internet has become an extraordinarily powerful resource for performing questionnaire-based research.

One of the most enticing, yet unexplored, medical applications of the Internet is the possibility of performing clinical trials on-line. Because of the vast scope of the Internet, it may be possible to study the attributes of various compounds which might otherwise never be evaluable in traditional clinic-based settings. An obvious application of the methodology would be to test a safe modestly-effective nutritional compound in the treatment of a common condition such as osteoarthritis, which is evaluable by means of validated self-reported questionnaires.

While questionnaire surveys abound on the Internet, there has been no exploration of the potential of this technology to evaluate an intervention. Further work is need to validate the validity of such an approach.

The aim of this study is to investigate the feasibility and validity of performing Internet-based clinical trials using the model of an on-line double-blind study of a glucosamine/chondroitin sulfate nutritional supplement for the treatment of symptoms associated with knee osteoarthritis. Specifically, we will (I) compare yields of different advertisement strategies (ii) describe the demographic characteristics of respondents (iii) measure the utility of the case-finding strategies (iv) validate disease status of Internet-derived cases ad questionnaire responses by means of in-person evaluations (v) document compliance with study capsules by means of pill diaries ad urine tests (vi) compare pain scores with those found in traditional settings.

15. RELEVANCE TO ARTHRITIS

Osteoarthritis (OA) is a major public health problems which imposes a considerable burden of pain, disability and expense among the elderly population. There are no proven medical remedies for this disorder, yet there exist a number of nutritional compounds, such as glucosamine, chondroitin, avocado/soybean derivatives, antioxidants and vitamins, which may be effective in relieving symptoms and possibly even reducing osteoarthritis progression. Unfortunately, because of the large numbers and huge costs involved in detecting efficacy from these compounds on OA, it is probable that most will never be adequately evaluated in traditional clinical trials. On the other hand, it is probable that such studies could be performed using the Internet. Our goal is to validate such an approach.

s this a "Quality of Lif " research project? Pleas check the appropriate box: ☒ Yes ☐ No
)uality of Life research is defined as research with th f llowing characteristics: 1) use of human subjects, and 2) incorporates linically relevant outcom measures, and 3) has as its primary focus the prevention, treatment, or management of rheumatic and nusculoskeletal disease.

EXHIBIT A - PAGE 3

DEFINITION OF ARTHRITIS FOUNDATION STUDY SECTIONS

Revised 4/03

Behavioral/Epidemiology/HSR studies include research on:
- ☐ epidemiology (clinical and population-based);
- ☐ clinical trials (behavioral, pharmacologic, surgical, and rehabilitative interventions)
- ☐ health services research (including utilization studies, economic studies, decision analysis, and outcomes);
- ☐ qualitative research and quality of life research;
- ☐ other evaluation research (including educational programs).

Biochemistry studies relating to the pathogenesis of arthritis are designed to:
- ☐ delineate basic biochemical pathways involved in cellular metabolism;
- ☐ investigate methods for the isolation and biochemical characterization of biological molecules;
- ☐ investigate enzymes involved in matrix degradation;
- ☐ study the role of cytokines and growth factors in cellular metabolism and/or signal transduction;
- ☐ study how biomechanical factors may influence cellular metabolism in rheumatic diseases.

Cell Biology studies are designed to understand:
- ☐ the function of cells besides those involved in the immune system;
- ☐ the biology of connective tissue cells such as fibroblasts, chondrocytes, osteoblasts;
- ☐ the physiology of intact organs or tissues such as bone and cartilage;
- ☐ abnormalities in the function of these cells and tissues in diseases states;
- ☐ the genetic basis of normal and abnormal function of connective tissue.

Cellular Immunology studies are designed to understand the cellular mechanisms of immune responses, including:
- ☐ development, function, and interactions of immune cells;
- ☐ lymphocyte activation and inactivation;
- ☐ regulation of immune responses.

Clinical Immunology studies are designed to understand the immunopathogenesis of the rheumatic diseases, including:
- ☐ immunologic abnormalities in patients with rheumatic diseases;
- ☐ genetic associations with rheumatic diseases;
- ☐ animal models of autoimmune diseases;
- ☐ immunopharmacology.

Inflammation studies are designed to understand:
- ☐ endothelial cell biology and leukocyte endothelial adhesion;
- ☐ fluid phase mediators of inflammation such as complement and acute phase reactants;
- ☐ biology of cytokines including their production and actions, but not the lymphocyte-related aspects of cytokine biology;
- ☐ activation mechanisms of neutrophils, monocytes, and other myeloid cells in inflammatory diseases.

Molecular Biology and Genetics studies are designed to:
- ☐ clone and sequence genes relevant to rheumatic disease;
- ☐ evaluate genetic structure;
- ☐ understand gene regulation;
- ☐ molecular studies of autoantibodies.

Molecular Immunology studies are designed to understand at a molecular level the immune system, including:
- ☐ structure-function relationships of molecules relevant to the immune response, for example, MHC antigens and immunoglobulins, T cell antigen receptors;
- ☐ the regulation of expression of genes encoding these molecules;
- ☐ signaling mechanisms of immune cell receptors.

Technologies/Biomechanics studies include research on:
- ☐ biomaterials;
- ☐ biomechanics;
- ☒ computing and medical informatics;
- ☐ technology (diagnostic and treatment).

EXHIBIT A - PAGE 4

16. KEY PERSONNEL

Name, Degree(s)	Position, Title, Role in Project	Department and Organization
Timothy McAlindon, BM, DM	Assistant Professor of Medicine, Principal Investigator	Dept. of Rheumatology, Boston University School of Medicine
Doreen Nicastro, MPH	Dir., Training & Communications Co-Investigator	Office of Information Tech. Boston University Medical Campus
Michael Paul LaValley, Ph.D.	Assistant Professor of Epidemiology and Biostatistics Statistician	Dept. of Epidemiology and Biostatistics, Boston University School of Public Health
To Be Named	Computer Programmer	
To Be Named	Research Assistant	
To Be Named	Systems Administrator	

EXHIBIT A - PAGE 5

17a. DETAILED BUDGET PROPOSAL FOR FIRST YEAR

EXPENDITURE CATEGORY					COSTS
A. SALARIES					
Name/Degree	*Position*	*% Time/ Effort*	*Salary*	*Soc. Sec. & Other Benefits*	
T. McAlindon	PI	25%	21,533	5,039	26,572
To Be Named	Res. Ass't	50%	12,500	2,438	14,938
To Be Named	Systems Adm.	15%	8,250	1,931	10,181
D. Nicastro	Co-Investigator	15%	9,450	2,211	11,661
To be Named	Comp. Prog.	20%	9,600	2,246	11,846
B. PERMANENT EQUIPMENT					
Micron Computer with upgrades					2,497
C. EXPENDABLE SUPPLIES					
See Budget Justification for details					500
D. TRAVEL (list)					0
E. OTHER EXPENSES (itemize) (See Budget Justification for details)					
Telephone	600				5,132
Express mailing: pills	500				
Advertising: 6@ $500 ea.	3,000				
Medical records	1,000				
Mailings	32				
F. TOTAL DIRECT COSTS					83,327
G. INDIRECT COSTS (not to exceed 8%)					6,666
H. TOTAL BUDGET FOR ONE YEAR					89,993

T. McAlindon

Signature of Principal Investigator

2/27/97

Date

EXHIBIT A - PAGE 6

17b. DETAILED BUDGET PROPOSAL FOR SECOND YEAR

EXPENDITURE CATEGORY					COSTS
A. SALARIES					
Name/Degree	Position	% Time/ Effort	Salary	Soc. Sec. & Other Benefits	
T. McAlindon	PI	25%	22,179	5,190	27,369
To Be Named	Res. Ass't	50%	12,875	2,511	15,386
To Be Named	Systems Adm.	15%	8,498	1,988	10,486
D. Nicastro	Co-Investigator	15%	9,734	2,278	12,012
To be Named	Comp. Prog.	20%	9,888	2,314	12,202
B. PERMANENT EQUIPMENT					0
C. EXPENDABLE SUPPLIES See Budget Justification for details					500
D. TRAVEL (list) ACR travel expenses for PI					1,000
E. OTHER EXPENSES (Itemize) (See Budget Justification for details)					
Advertising 4 @ $500 ea.	2,000				4,132
Express mail: pills	500				
Medical records	1,000				
Mailings	32				
Telephone expenses	600				
F. TOTAL DIRECT COSTS					83,087
G. INDIRECT COSTS (not to exceed 8%)					6,647
H. TOTAL BUDGET FOR ONE YEAR					89,734

T.E. McAlindon

Signature of Principal Investigator

2/27/02

Date

EXHIBIT A - PAGE 7

17c. DETAILED BUDGET PROPOSAL FOR THIRD YEAR

EXPENDITURE CATEGORY					COSTS
A. SALARIES					
Name/Degree	*Position*	*% Time/ Effort*	*Salary*	*Soc. Sec. & Other Benefits*	
T. McAlindon	PI	25%	22,844	5,346	28,190
To Be Named	Res. Ass't	50%	13,261	2,586	15,847
To Be Named	Systems Adm.	15%	8,752	2,048	10,800
D. Nicastro	Co-Investigator	15%	10,026	2,346	12,372
M. LaValley	Statistician	5%	3,044	712	3,756
To be Named	Comp. Prog.	15%	7,638	1,787	9,426
B. PERMANENT EQUIPMENT					0
C. EXPENDABLE SUPPLIES					
See Budget Justification for details					500
D. TRAVEL (list)					
ACR travel expenses for PI					1,000
E. OTHER EXPENSES (itemize)					
Telephone 600					600
F. TOTAL DIRECT COSTS					82,491
G. INDIRECT COSTS (not to exceed 8%)					6,599
H. TOTAL BUDGET FOR ONE YEAR					89,090

T E McAlindon

Signature of Principal Investigator

8/21/02

Date

Budg t Justification: Personnel Costs

(annual increases @ 3%)

1. Tim McAlindon MD MPH, Primary Investigator (25%). Dr. McAlindon will oversee the scientific and administrative aspects of the study including supervision of the Website, collection and management of the data, and acquisition of medical records. He will be one of the reviewers of medical records, and will be closely inv lved with all statistical analyses. He will prepare and submit the manuscript resulting from the study.

2. Doreen Nicastro, Co-Investigator, Director of The Office of Information Technology, Boston University School of Medicine (15%). Doreen Nicastro will be responsible for overseeing the technologic aspects of the study, and the development of the Website. She will supervise the activities of the Computer Programmer and Systems Administrator.

3. *To Be Named*, Computer Systems Administrator (15%) plays a key function in this project. He/she will participate in the construction of the Website, particularly in relation to its spatial and operational incorporation within the framework of the institution's Website. This is a complex and sophisticated task which requires this level of skilled continuing support. He/she will also be responsible for maintenance and continuing development of the site.

4. To be named, Computer/Web Programmer (20% years 1,2; 15% year 3, reflecting decreased activity) will be responsible for designing, constructing and operationalizing the dynamic aspects of the web site. This includes incorporation of interactive modules (e.g. java applets for visual analog scales), development of programs for real-time data quality monitoring, generation of automated responses, and data processing capabilities so that data can be collected into analyzable datasets.

5. *To Be Named*, Research Assistant (50%) will be based at the Arthritis Center, Boston University School of Medicine, under the direct supervision of Dr. Timothy McAlindon. He/she will be responsible for the administrative aspects of the study. This will involve arranging and constructing various forms of advertisements and Internet links, contacting respondents and participants by Email, conventional mail, and phone, answering calls, writing to hospitals and physicians to obtain radiographs or copies of their reports, tracking responses and maintaining a basic database.

6. Michael LaValley, Statistician, 5% year 3. Michael LaValley will supervise the analyses in year 3.

Budget Justification: Non-Personnel Costs

Year 1

Supplies	
General office supplies, stationary, diskettes, printing, copying	$400
Microsoft FrontPage license fees (2 @ 50 each):	$100
Other	
Telephone expenses	$600
Sending capsules to participants by express mail (50 @ $10)	$500
Advertising costs (6 adverts @ $500 each)	$3000
Cost of obtaining copies of medical records:	
Institutional charges (100 @ $10)	$1000
Mailing costs (100 @ $0.32)	$32

EXHIBIT A - PAGE 9

Equipment	
Computer for Research Coordinator	
Micron Millenia 400 with upgrade	$2497
Year 2	
Supplies	
General office supplies, stationary, diskettes, printing, copying	$ 400
Microsoft FrontPage license fees (2 @ 50 each):	$100
Travel	
Attendance at Annual Meeting of the American College of Rheumatology	$1000
Other	
Telephone expenses	$600
Sending capsules to participants by express mail (50 @ $10)	$500
Advertising costs (4 adverts @ $500 each)	$2000
Cost of obtaining copies of medical records:	
Institutional charges (100 @ $10)	$1000
Mailing costs (100 @ $0.32)	$32
Year 3	
Supplies	
General office supplies, stationary, diskettes, printing, copying	$400
Microsoft FrontPage license fees (2 @ 50 each):	$100
Travel	
Attendance at Annual Meeting of the American College of Rheumatology	$1000
Other	
Telephone expenses	$600

EXHIBIT A - PAGE 10

TOR RAYTHEON
MICRON SYSTEMS
PPLICATIONS.
'HIN BUDGET)

/hat Micron has delivered

for years. By preconfiguring systems to perfectly meet highly specialized n eds while keeping our prices low to meet the budget of any we offer the perfect solution for nding user. If you're looking for that are as powerful as a fighter reliable as a trained soldier, ser look at the Micron Millennia.® We think you'll soon see why thos whose lives depend on their computers depend on Micron.

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dBench of 210."
'id, "Best Buy," July '98

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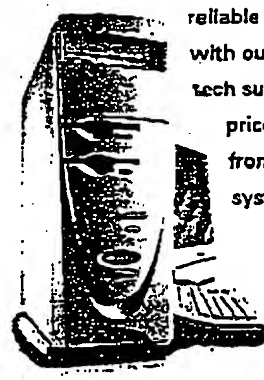
When power users want performance desktops, they turn to Micron. And judging from their response, they're impressed. Perhaps that's because Micron offers the power of a 400MHz machine that *PC World* rated faster than any other 400MHz system they tested. But power is not enough. Which is why Micron builds every system using only the finest quality, most reliable components and backs them up with our responsive and knowledgeable tech support and sales force - all at prices you wouldn't expect to find from a top-tier $2 billion direct systems manufacturer.



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Millennia® 266	Millennia 350	Millennia 400
• Intel Pentium® II processor 266MHz	• Intel Pentium II processor 350MHz	• Intel Pentium II processor 400MHz
• 32MB SDRAM	• 64MB PC100 SDRAM	• 64MB PC100 SDRAM
• 4.3GB Ultra ATA hard drive	• 6.4GB Ultra ATA hard drive	• 6.4GB Ultra ATA hard drive
• 15" Micron 500Lx, .28dp(13.7" display)	• 17" Micron 700FGx, .26dp(16" display)	• 17" Micron 700FGx, .26dp(16" display)
• 82440LX chip set	• 82440BX chip set	• 82440BX chip set
• 512KB internal cache, 2MB flash BIOS	• 512KB internal cache, 2MB flash BIOS	• 512KB internal cache, 2MB flash BIOS
• 3.5" floppy drive	• 3.5" floppy drive	• 3.5" floppy drive
• 32X EIDE variable speed CD-ROM drive	• 32X EIDE variable speed CD-ROM drive	• 32X EIDE variable speed CD-ROM drive
• 128-bit AGP Diamond Viper V330 (nVidia), 4MB EDO SGRAM & MPEG	• 128-bit AGP Diamond Viper V330 (nVidia), 4MB EDO SGRAM & MPEG	• 128-bit AGP Diamond Viper V330 (nVidia), 4MB EDO SGRAM & MPEG
• Integrated 32-voice Wavetable 3D stereo sound	• Integrated 64-voice Wavetable 3D stereo sound	• Integrated 64-voice Wavetable 3D stereo sound
• Advent AV009 stereo speakers	• Advent AV009 stereo speakers	• Advent AV009 stereo speakers
• 56K data/fax modem*	• 56K data/fax modem*	• 56K data/fax modem*
• 104-key enhanced keyboard	• 104-key enhanced keyboard	• 104-key enhanced keyboard
• Microsoft® IntelliMouse®	• Microsoft IntelliMouse	• Microsoft IntelliMouse
• Microsoft Windows® 98'	• Microsoft Windows 98'	• Microsoft Windows 98'
• Microsoft Office 97 Small Business Edition	• Microsoft Office 97 Small Business Edition	• Microsoft Office 97 Small Business Edition
• 5-year/3-year Micron Power™ limited warranty	• 5-year/3-year Micron Power limited warranty	• 5-year/3-year Micron Power limited warranty
$1,479 Bus. Lease $52/mo.	**$2,099** Bus. Lease $73/mo.	**$2,199** Bus. Lease $77/mo.
UPGRADE TO:	UPGRADE TO:	UPGRADE TO:
• 8.4GB Ultra ATA hard drive	• 8.4GB Ultra ATA hard drive	• 8.4GB Ultra ATA hard drive
• Iomega 100MB Zip drive	• Iomega 100MB Zip drive	• Iomega 100MB Zip drive
• 17" Micron 700FGx, .26dp (16" display)	• DVD-ROM drive and PCI decoder card**	• DVD-ROM drive and PCI decoder card**
$1,846 Bus. Lease $65/mo.	**$2,397** Bus. Lease $84/mo.	**$2,497** Bus. Lease $87/mo.

*Maximum transmission speed of up to 56Kbps when downloading data and 33.6Kbps when uploading. However, actual performance is dependent upon numerous factors and observed transfer rates may be less than the maximum possible. **The CD-ROM drive will be removed upon the purchase of the DVD-ROM drive upgrade. Windows 98 is subject to availability.

MICRON ELECTRONICS

EXHIBIT A - PAGE 11

FF Principal Investigator/Program Director (Last, first, middle): McAlindon, Timothy

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Timothy E. McAlindon	Assistant Professor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Southampton University Medical School, UK	B.M.	1982.	Medicine
Southampton University Medical School, UK	D.M.	1993	Medicine
Boston University School of Medicine, USA	M.P.H.	1995	Public Health

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

CAREER OUTLINE

Currently:		
1995-present	Assistant Professor of Medicine	Boston University School of Medicine Boston, Massachusetts USA
nternships:		
1982-83	House Physician	Royal United Hospital, Bath, UK
1983-83	House Surgeon	Queen Elizabeth Hospital, Birmingham, UK
esidencies:		
1983-84	SHO in ER	The Royal Hospital, Wolverhampton, UK
1984-95	Internal Medicine SHO	Torbay Hospital, Torquay, UK
1985-88	Medical Registrar	Southmead Hospital, Bristol, UK
ellowships:		
1988-90	Arthritis & Rheumatism Council Research Fellow in Rheumatolog	Bristol Royal Infirmary, Bristol, UK
1990-95	Senior Registrar in Rheumatology & General Medicine	St. Thomas' Hospital, London, UK
1993-95	Arthritis & Rheumatism Council Visiting Research Fellow	Arthritis Center, A203, BU Med. Ctr. Boston, MA 02118

PUBLICATIONS

McAlindon TE. Disseminated intravascular coagulation followingphenelzine overdose. BMJ 1986;293:1103.
McAlindon TE, Ferguson IT. Mononeuritis multiplex and occipital infarction complicating giant celbrteritis. British J Rheumatol 1989;28:257-8.
McAlindon TE, Dieppe PA. Osteoarthritis: definitions and criteria. (Leading Article) Ann Rheum Dis 1989;48:531-2.
McAlindon TE, Dieppe PA. Arthritis in the elderly. Medicine International 1990;74:3095-8.
McAlindon TE, Dieppe PA. The medical management of osteoarthritis of the knee : an inflammatory issue ? (Viewpoint) Brit J Rheum 1990;29:471-473.
McAlindon TE, Dieppe PA. Osteoarthritis. Care of the Elderly 1990;2:201-203.
McAlindon TE, Dieppe PA. Disorders f the shoulder in elderly people (letter) Brit Med J 1990;300:1341.

EXHIBIT A - PAGE 12

FF Principal Inv - ator/Program Director (Last, first, middle): McAlindon, Timothy

Cushnaghan J, Cooper C, Dieppe P,Kirwan J, McAlindon T, McCrae F. Clinical assessment of steoathritis of the knee. Ann Rheum Dis 1990;49:768-770.

Seegmiller JE, Dixon RM, Kemp GJ, Angus PW,McAlindon TE, Dieppe P, Rajgopalan B, Radda GK. Fructose-induced aberration of metabolism in familial gout identified by 31P magnetic resonance spectroscopy. Proc Natl Acad Sci USA 1990;87:8326-8330.

0 McAlindon TE, Watt I, McCrae F, Goddard P, Di pp PA. Magnetic resonance imaging in osteoarthritis of the knee : correlation with radiographic andscintigraphic findings. Ann Rheum Dis 1991;50:14-19

1 McAlindon TE, Cooper C, Kirwan JR, Dieppe PA. Knee pain and disability in the community. British Journal of Rheumatology 1992;31:189 - 192

2 McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of thepatello-femoral joint. Ann Rheum Dis 1992;51:844-9

3 Cooper C, Cushnaghan J, Kirwan JR, Dieppe PA, Rogers J,McAlindon TE, McCrae F. Radiographic assessment of the knee joint in osteoarthritis. Annals Rheum Dis 1992;51:80-82.

4 Dieppe P, Cushnaghan J, McAlindon T. Epidemiology, clinical course and outcome of knee osteoarthtis. In - Articular cartilage and Osteoarthritis, SDKuettner et al, Raven Press, New York 1992.

5 McAlindon TE, Teal D, Dieppe PA. Insulin-like Growth Factor 1 levels in osteoarthritis of the knee. Annals Rheumatic Diseases 1993;52:229-31

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7 Hanson JA, McAlindon TE. Possible Dangers of cold water.Brit J Rheumatol 1993;32:525-6

8 Jones AC, Ledingham J, McAlindon T et al. Radiographic assessment ofpatellofemoral osteoarthritis. Annals of the Rheumatic Diseases 1993;52:655-658

9 McAlindon TE, Giannotta L, Taub N, D'Cruz D, Hughes G. Environmental factors predicting nephritis in SLE. Annals of the Rheumatic Diseases 1993;52:720-724

0 McAlindon TE, MacFarlane D, Ward S, Mathews JA. Transient regional osteoporosis presenting as a septic arthritis. Postgraduate Medical Journal 1993;69:871-873

1 Cooper C, McAlindon TE, Snow S et al. Mechanical and constitutional risk factors for symptomatic knee OA: differences between medial tibiofemoral and patellofemoral disease. J Rheumatol 1994;21:307-13

2 Cooper C, McAlindon TE, Coggon D et al. Occupational activity and osteoarthritis of the knee. Annals of the Rhematic Diseases 1994;53:90-93

3 McAlindon TE, Hannan MT, Felson DT et al. Are risk factors forpatellofemoral and tibiofemoral knee osteoarthritis different? J Rheumatol 1996;23:332-7

4 Chaisson C, McAlindon TE, Felson et al. Relationship of thyroid status to knee OA andchondrocalcinosis in the Framingham study. J Rheumatol 1996;23:711-5

5 McAlindon TE, Jacques P, Zhang Y,Hannan MT, Aliabadi P, Weissman B, Rush D, Levy D, Felson DT. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? Arthritis Rheum 1996;39:648-656

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7 McAlindon TE, Felson DT. Identifying individuals at risk for arthritis. IM Internal Medicine 1996;17:17-28

8 Lloyd ME, Hart D, Nandra D, McAlindon T, Wheeler D, Doyle D, Spector TD. The relationship of IGF-1 levels, osteoarthritis and bone density: TheChingford Study. Annals Rheumatic Disease - In press.

9 Felson DT, McAlindon TE, Anderson JJ, Naimark A, Weissman BW, Aliabadi P, Evans S, Levy D, LaValley MP. Defining radiographic osteoarthritis for the whole knee. Osteoarthritis & Cartilage 1997;5:241-50.

0 McAlindon TE, Felson DT. Nutritional risk factors for knee osteoarthritis. (Leading Article) In press - Ann Rheum Dis. (Leading Article) Ann Rheum Dis July 1997.

1 Chaisson CE, Zhang Y, McAlindon TE, Hannan MT, Aliabadi P, Naimark A, Levy D, Felson DT. Radiographic hand osteoarthritis: incidence, patterns, and influence of pre-existing disease in a population-based sample. J Rheum 1997;24:1337-43

2 Kauppila LI, McAlindon T, Evans S, Wilson PWF, Kiel D, Felson DT. Disc degeneration, back pain and calcification of the abdominal aorta. Spine 1997;22:1642-7

3 McAlindon TE, Felson DT. Nutritional risk factors for knee osteoarthritis. (Leading Article) Ann Rheum Dis 1997;56:397-402

EXHIBIT A - PAGE 13

Principal Investigator/Program Director (Last, first, middle): McAlindon, Timothy

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Michael LaValley	Statistician

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
American International College	B.A.	1984	Mathematics & Philosophy
Ohio State University	M.S.	1985	Mathematics
Pennsylvania State University	Ph.D.	1993	Statistics

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

CAREER OUTLINE

1986-1988 Math and Science Teacher Trainer, U.S. Peace Corps, Science Education Development Project o Nepal
1989-1992 Graduate Assistant, Pennsylvania State University, Department of Statistics
1992-1993 Instructor, Pennsylvania State University, Department of Statistics
1993-1995 Postdoctoral Research Fellow, Harvard School of Public Health, Department of Biostatistics
1995 - Assistant Professor of Epidemiology and Biostatistics, Boston University School of Public Health, Department of Epidemiology and Biostatistics; Boston University School of Medicine, Arthritis Center, Health Services/Epidemiology Unit.

PUBLICATIONS

Akritas M, Murphy S, LaValley M: The Theil-Sen estimator with doubly censored data and applications to astronomy. JASA 90:170-177, 1995.
Akritas M, LaValley M: Nonparametric inference in factorial designs with censored data. Biometrics 52:913-924, 1996.
LaValley M, DeGruttola V: Models for empirical bayes estimators of longitudinal CD4 counts. Statistics in Medicine 15:2289-2305, 1996.
Akritas M, LaValley, M: Statistical analysis of incomplete data: a selective review. In The Handbook of Statistics: Robust Inference, G.S. Maddala and C.R. Raoeds, Elsevier Science, 51-632, 1997.
LaValley M: A consumers guide to meta-analysis. Arthritis Care and Research 10:208213, 1997.
Felson D, McAlindon T, Anderson J, Naimark A, Weissman B, Aliabadi P, Evans S, Levy D, LaValley M: Defining radiographic osteoarthritis for the whole knee. Osteoarthritis and Cartilage 5:241-250, 1997.
Dubrey S, Cha K, Skinner M, LaValley M, Falk R: Familial and primary (AL) cardiac amyloidosis: Echocardiographically similar diseases with distinctly different clinical outcomes. Heart 78:74-82,1997.
Reisinger J, Dubrey S, LaValley M, Skinner M, Falk R: Electrophysiologic abnormalities in primary amyloidosis (AL) with cardiac involvement. Journal of the American College of Cardiology 30:1046-1051, 1997.
LaValley M, Anderson J: Statistical and study design issues in assessing the quality and outcomes of care in rheumatic diseases. Arthritis Care and Research 10:431-440, 1997.
Dubrey S, Bilazarian S, LaValley M, Skinner M, Falk R: Signal-averaged electrocardiography in patients with AL (primary) amyloidosis. American Heart Journal, 134:994-1001, 1997.

1. Comenz R, Vosburgh E, Falk R, Sanchorawala V, Reisinger J, Dubrey S, Dember L, Berk J, Akpek G, LaValley M, O'Hara C, Arkin C, Wright D, Skinner M: Dose-intensive melphalan with blood stem-cell support for the treatment of AL amyloidosis: Survival and responses in 25 patients. Blood, 91:3662-70, 1998.
2. Fraenkel L, LaValley M, Felson D: The use of radiographs to evaluate shoulder pain in the emergency department. The American Journal of Emergency Medicine, in press.
3. Felson D, Couropmitree N, Chaisson C, Hannan M, Zhang Y, McAlindon T, LaValley M, Levy D, Myers R: Evidence for a mendelian gene in a segregation analysis of generalized radiographic ost oarthritis: The Framingham Study. Arthritis & Rheumatism, 41:1064-71, 1998.
4. Fraenkel L, LaValley M, McAlindon T, Chaisson C, Roubenoff R, Dinarello C, Harris T, Felson D: The association of peripheral monocyte derived interleukin 1beta and tumor necrosis factor alpha with osteoarthritis. Journal of Rheumatology, in press.
5. Fraenkel L, Zhang Y, McAlindon T, LaValley M, Trippel S, Assif A, Adams K, Felson D: Longitudinal analysis of the relationship between serum insulin-like growth factor-1 and radiographic knee osteoarthritis. Osteoarthritis and Cartilage, in press.
6. Felson D, Anderson J, Lange M, Wells G, LaValley M: Should improvement in rheumatoid arthritis clinical trials be defined as fifty percent or seventy percent improvement in core set measures, rather than twenty percent? Arthritis & Rheumatism, in press.
7. LaValley M, Isobe T, Feigelson E: ASURV: Astronomy survival analysis package, *in* Astronomical Data Analysis Software and Systems I, eds Worrall, et al, Astronomical Society of the Pacific Conference Series, 25:245-247, 1992.
8. LaValley M, Isobe T, Feigelson E: ASURV: Bulletin of the American Astronomical Society, 1992.
9. LaValley M, Akritas M, Feigelson E: Applications of a generalized Kaplan-Meier estimator to astronomical data sets, IMS Bulletin, 20, 268, 1991.
0. LaValley M, Akritas M: Extensions of the Lynden-Bell Woodroofe method for truncated data. Submitted.

EXHIBIT A - PAGE 15

F Principal Inver tor/Program Director (Last, first, middle): McA" don, Timothy

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel in the order listed on Form Page 2.
Photocopy this page or follow this format for each person.

NAME	POSITION TITLE
Doreen A. Nicastro	Director of Training and Communications

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training).*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Suffolk University	B.S.	1980	Criminal Justice
Boston University School of Public Health	M.P.H.	1989	Public Health

RESEARCH AND PROFESSIONAL EXPERIENCE: Concluding with present position, list, in chronological order, previous employment, experience, and honors. Include present membership on any Federal Government public advisory committee. List, in chronological order, the titles, all authors, and complete references to all publications during the past three years and to representative earlier publications pertinent to this application. If the list of publications in the last three years exceeds two pages, select the most pertinent publications. DO NOT EXCEED TWO PAGES.

CAREER OUTLINE

982-1984 Senior Research Assistant, Boston University School of Public Health
984-1985 Special Assistant to Associate Director, Boston University School of Public Health
985-1989 Systems Specialist, Boston University School of Public Health
989-1992 Assistant Director, Boston University Medical Center, Office of Information Technology
992-1995 Head of Educational Computing and Learning Resources, Boston University Medical Center, Alumni Medical Library
995-1997 Director, Biomedical Information Technology Program, Boston University Medical Center, Division of Graduate Medical Sciences
997- Director of Training and Communications, Boston University Medical Center, Office of Information Technology

PUBLICATIONS

Markson, L., Nicastro, D., Kern, D., Culbert, A., Using Medical Diagnostic Software as a Teaching Aid in a Home Care Setting, Journal of Medical Education Technologies Vol. (4) (4): 23-26, 1994.

Markson, L., Nicastro, D., Kern, D., Culbert, A., Using Medical Diagnostic Software as a Teaching Aid in a Home Care Setting, Presented at the Sixth Annual Conference: Society for Applied Learning Technology in Health Care Science, February 26-28, 1992, Orlando, Florida.

Nicastro, D., Culbert, A., Cantelmo, N., Stafford, M., Levenson, S., The Use of Interactive Video as Part of the Medical School Curriculum, Presented at the Fifth Annual Conference: Society for Applied Learning Technology in Health Care Science, February 20-22, 1991, Orlando, Florida.

Meyers AR, Cupples A, Lederman R, Branch L, Feltin M, Master R, Nicastro D, Glover M, Kress D, The Epid miology of Medical Care Utilization by Severely Disabled Independently-Living Adults, Journal of Clinical Epidemiology, Vol. 41:163-172. 1988.

Meyers AR, Cupples A, Lederman RI, Branch LF, Feltin M, Master RJ, Nicastro D, Glover M, Kress D, A Prospective Evaluation of the Effects of Managed Care on Medical Care Utilization Among Severely-Disabled Independently-Living Adults. Medical Care Vol. 25: 1057-1068. 1987.

Meyers AR, Feltin M, Master RJ, Nicastro D, Cupples A, Lederman RI, Richard LH, (1985). Hospitalization and Spinal Cord Injury: a cross-sectional survey of independently living adults. Archives Physical Medicine and Rehabilitation, Vol. 66: 705-708. 1985.

19. Concurrent Support

MCALINDON, T.

ACTIVE

AR20613 (Felson) NIH/NIAMSD Arthritis and Musculoskeletal Diseases Center	09/17/97 - 08/31/01 $940,435	50%

This is a multiproject grant supporting biomedical and non-biomedical research. The Core B Unit is a central resource for health services research, epidemiology and computer-based data analysis.

Bayer Corporation	02/01/97-06/30/99 $81,689	15%

This study investigates the safety, tolerability and efficacy of bay 12-9566 as compared to placebo, in the treatment of patients with mild to moderate osteoarthritis of the knee.

Lupus Foundation	10/01/97-09/30/99 $30,000	10%

This study investigates the potential Utility of Indole-3-Carbinole supplements in the therapy of rheumatic diseases

PENDING

None

OVERLAP

There is no scientific overlap with these or any other funded projects.

19. Concurr nt Support M^ALINDON, TIMOTHY

LAVALLEY, M.

ACTIVE

AR20613 (Felson)	09/17/1/97 - 08/31/01	60%
NIH/NIAMSD	$940,435	

Arthritis and Musculoskeletal Diseases Center

This is a multiproject grant supporting biomedical and non-biomedical research. The Core B Unit is a central resource for health services research, epidemiology and computer-based data analysis.

Arthritis Foundation (Allaire)	07/01/96 - 06/30/99	5%
Arthritis Foundation	$62,748	

Increasing use of the Americans with Disabilities Act by persons with arthritis: An educational diagnosis

The major goal is to determine which factors should be addressed by interventions to enable persons with arthritis successfully use the antidiscrimination and reasonable accommodation rights ensured by the Americans with Disabilities Act.

FD-R-001346-01 Comenzo)	9/01/96 - 8/31/99	5%
FDA	$111,410	

A phase II trial of a new therapy of AL amyloidosis

This grant supports a randomized phase II clinical trial of done-intensive intravenous melphalan at diagnosis or after two doses of oral chemotherapy for patients with primary (AL) amyloidosis.

PENDING

None

OVERLAP

N/A

EXHIBIT A - PAGE 18

20. RESOURCES AND ENVIRONMENT

FACILITIES: Mark the facilities to be used at the applicant organization and briefly indicate their capacities, pertinent capabilities, relative proximity and extent of availability to the project. Use "other" to describe the facilities at any other performance sites and at sites for field studies. Using continuation pages if necessary, include an explanation of any consortium/contractual agreements with other organizations.

☐ Laboratory:

☐ Clinical:

☐ Animal:

☒ Computer:

Dr McAlindon's office computer: Dell Optiplex Pentium computer with 64 MB RAM and 6 GB hard disk, running Windows 95. This computer has PC SAS 6.12, S-Plus 4.5 and Microsoft Office 97 and Microsoft Frontpage installed.

☒ Office:

Copy and fax machine.

☐ Other:

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

Please see 'additional information' below about our Office of Information Technology

ADDITIONAL INFORMATION: Provide any other information describing the environment of the project. Identify support services such as consultants, secretaries, machine shop, and electronics shop, and the extent to which they will be available to the project.

Dr. McAlindon's office computer is network linked to the Boston University Medical Center's Digital Alpha2 (UNIX) computer with mainframe SAS 6.10 installed, and to the Academic Computing System, a network of IBM RS/60-0 990 (AIX) computers. In addition, the computer is linked to the Windows server for the Medical Campus, allowing good computer support and automatic back-up of files. A HP laserjet and deskjet color printers are located in main arthritis center office.

Boston University Office of Information Technology (OIT)

Boston University Office of Information Technology (OIT) primary focus is on facilities and services addressing needs of the entire Medical Campus. The OIT will also support special needs of individual schools, departments, and research centers through specific arrangements. OIT provides technology infrastructure, central-computing resources, such as print and file services. OIT offers the capacity for collaborative computing, departmental web services and network-based general application training. A detail of the resources and services available to BUMC departments schools, staff and faculty is located at our department web site: http://www.bumc.bu.edu/bumc/oit/. (*Continued on following page*).

20. Resources and Environment (conti. 1)

Over the past two years, under the direction of OIT, Boston University Medical Campus has embarked on a strategic plan to upgrade and standardize the campus network. The goal is for increased speed, bandwidth and reliability to support the clinical, education, research and administrative mission of the schools of medicine, public health and dental medicine.

The first phase of the information technology plan includes cabling, using 'category 5" copper wire to every desktop location and fiber optic cable between every network connection device. These includes increasing bandwidth and reliability, providing capability carry video conferencing signals, and making network navigation less difficult for medical campus users.

The plan includes upgrading computing resources by creating and managing central servers that deliver data to the network at high speeds for many simultaneous users. Currently, the Office of Information Technology provides central computing facilities to the faculty and staff. These resources comprise three high-capacity Digital Alpha Servers, three Intel-based servers, and several general-purpose systems. The three Intel machines are functionally configured to provide central services for the Web; database services, via SQL Server; and system management services, to provide economies scale to Desktop Support, a division within OIT, in managing the enterprise.

As part of the strategic plan, the Office of Information Technology established the Desktop Computer Support Group. In order to provide a seamless information infrastructure in a cost effective and reliable manner, the Desktop Support Group focuses its efforts on the support of a standardized desktop configuration. The Desktop Computer Support Group functions as a Boston University Medical Campus Service Center. The operation of the Desktop Support Group as a Service Center is intended to provide the BUMC community with effective delivery and management of technical computer support and related information services while maintaining a fiscal responsibility based in cost recovery. Services include access to the OIT Help Desk, Consultative Services, Technical Services, access to subscription support program and annual client licenses.

BUMC schools, departments, faculty and staff have access to a high-speed enterprise network made up of online resources including, high performance central servers, collaborative computing, email resources, web services and general application training. In addition, a Support Center was established to provide high quality support and consultative services at competitive pricing.

BUMC OIT has expanded the information infrastructure of the campus by providing technical expertise and vision in the implementation of the first phase of the IT 2000 report. OIT is ready to work with schools, departments, staff and faculty to create a viable, reliable intranet supporting research and administration, clinical and educational activities. The infrastructure is in place and is supported through the Office of Information Technology. OIT is actively working with departments, schools, projects and centers within the medical campus to share in the cost of creating online databases, clinical, research and administration over the campus intranet.

EXHIBIT A - PAGE 20

21. ARTHRITIS FOUNDATION RESEARCH AWARD ASSURANCES

Principal Investigator's Full Name: Timothy E. McAlindon	Social Security Number: ~~017-78-1444~~

Title of Research Project:

A Study Of The Feasibility Of Internet-Based Clinical Trials In Osteoarthritis

TO BE COMPLETED BY SUPERVISING INSTITUTION: Will any of the following be used in this project?

☒ Human Subjects? ☐ Animal Subjects? ☐ Recombinant DNA? ☐ Biohazards?

Sponsoring Institution:

Boston University

CERTIFICATION AND ACCEPTANCE

The following statements are signed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this clause: The (institution) Trustees of Boston University agrees, if an Arthritis Foundation Award is given to (P.I.) Timothy Edward McAlindon and if human or animal subjects are used in any of the activities supported by such, that it will comply with all applicable U.S. Department of Health and Human Services' regulations with respect to the rights and welfare of such subjects.

The institution acknowledges and agrees that the work to be performed pursuant to this award is the responsibility of the institution; that the institution shall be responsible for any and all claims that may arise out of or in connection with such work; that the Arthritis Foundation shall have no responsibility for or to the subjects involved; and, to the full extent permitted by law, that the institution shall indemnify and hold the Arthritis Foundation harmless from and against any and all claims, liabilities and/or expenses arising from or related to this award and the work performed pursuant thereto.

APPROVAL BY DEAN OR HEAD OF INSTITUTION ON BEHALF OF INSTITUTION

Barbara A Cole 8/26/03

Signature Date

Barbara A. Cole

Above Name (typed)

Executive Director for Financial Affairs

Title

22. **RESEARCH PLAN:** Number continuation pages starting with 11. Add Renewal (#23) or Resubmission (#24) information, if applicable.

A. Specific Aims

The explosive growth in Internet use during the last few years has made it possible to communicate with greater numbers of people on-line than with any other technology. Recent software advances have made it possible to transmit and collect secure data from remote individuals over the Internet in an efficient and interactive manner. Thus, the internet has become an extraordinarily powerful resource for performing questionnaire-based research.

One of the most enticing, yet unexplored, medical applications of the Internet is the possibility of performing clinical trials on-line. Because of the vast scope of the Internet, it may be possible to study the attributes of various compounds which might otherwise never be evaluable in traditional clinic-based settings. For example, there exist a number of nutritional compounds which may be modestly effective in relieving osteoarthritis symptoms. Because of the large numbers and prohibitive costs involved in detecting efficacy from these compounds, it is unlikely that they will all be adequately evaluated in traditional clinical trials. The Internet, on the other hand, using validated symptom questionnaires, could have great utility in testing these safe compounds in the treatment of osteoarthritis.

On the other hand, there are many things that we need to learn about the Internet before such a study could be undertaken. Factors which may be critical to the feasibility of Internet-based trials include response rates, the demographic characteristics of respondents, willingness of respondents to participate, validity of responses, protocol compliance, and participant retention. We need to systematically evaluate these variables to determine the optimal trial design. Our aim, therefore, is to investigate these issues by performing a *model* on-line trial of a glucosamine/ chondroitin sulfate nutritional supplement among individuals with symptomatic knee osteoarthritis. Please note that we have not designed or powered this study to determine the *effectiveness* of glucosamine/ chondroitin sulfate. Our specific aims are as follows:

1. We will construct a web site providing a description of an Internet-based clinical trial of a glucosamine hydrochloride / chondroitin sulfate combination in the treatment of knee osteoarthritis. This site will include a solicitation for participants, and screen for knee osteoarthritis using validated questions.

2. We advertise the study web site using four different approaches (i) Internet-based, health-related [e.g. advertisements, links, on Arthritis Foundation web site] (ii) Internet-based, non-health related [e.g. advertisements, links, on other web sites] (iii) non-Internet, health-related [e.g. advertisement in Arthritis Foundation newsletter] (iv) non-Internet, non-health related [e.g. advertisement in magazine for Internet].

3. We confirm disease status by obtaining copies of medical records and performing chart abstraction using a validated algorithm for knee OA.

4. We will recruit respondents over the Internet into a 14-week *model* double-blind randomized trial of a glucosamine hydrochloride / chondroitin sulfate combination. Over the Internet, participants will complete validated pain assessment questions, submit daily analgesic use data and pill counts, and report adverse events.

5. We will (i) compare the utility of the different advertisement strategies (ii) describe the numbers and demographic characteristics of respondents and participants (iii) measure compliance and completion rates (iv) compare pain score distributions with those found in traditional settings (v) estimate the cost of a fully-powered Internet-based clinical trial.

B. Background

Potential Of The Internet To Serve As A Vehicle For Performing Clinical Studies

The explosive growth of the Internet during the last few years represents one of the most remarkable phenomena of the 1990s. As the number of users increases exponentially, the so-called information highway promises to revolutionize the way we conduct our lives and daily business. One commercial survey in 1997 indicated that there are 52 million Internet users in the U.S., 43% of whom are women[1]. At the time of the survey, 30 million persons had used the Internet in the previous 24 hours. The demography of respondents suggests that most users are middle class or higher - 80% own or lease a home computer, 77% have a credit card in their name, 49% have at least a college associate degree and 46% live in households with total annual income over $50,000. The Internet is rapidly becoming part of the population's daily activities. Indeed, a survey by the Emerging Technologies Research Group of FIND/SVP found that more than twenty million Americans have come to view the Internet as an "indispensable" part of their lives. They estimated that during April 1997, business users spent 5.75 hours per person on the Web, and home users spent 3.5 hours.

The Graphic, Visualization and Usability Center (GVU) has performed 5 annual surveys of non-random Internet users since 1994[2]. Their results are based on individuals responding to solicitations and are likely to be applicable to individuals responding to advertisements to participate in a clinical trial. In their 1997 survey, the average age of all Web users was 33 years. However, over 10% of users were aged over fifty years, representing about 6 million individuals. Overall, 31.5% of the users were female (a slightly lower figure than that reported by FIND/SVP).

There appear to be only minor differences in patterns of Internet use between individuals aged over 50 and younger users. All age groups are equally likely to use other Web pages and search engines to find new Web pages. One finding of importance for this proposal is that respondents aged 50 and over spend 7 to 20 hours per week on the Web - second only to the youngest users, who spend over 21 hours per week. Among those aged over 50, 74.3% use the web at least several times a week compared to 60.0% of those aged 26-50 and 57.4% of those aged 19-25. Older users are more inclined to use the Web instead of watching TV, and tend to access newsgroups more frequently than younger respondents: 22.8% access them at least once a day. Also, older respondents are more likely to find out about Web pages through traditional media: magazines (71.6%), newspapers (56.7%), TV (37.8%), and books (31.8%). A proportion of respondents also reported providing false registration information at times when logging into web sites. This was most marked among younger individuals, and decline with increasing age: 32.0% for 19-25 years old, 25.0% for 26-50 years old, and 13.6% for those over 50 years old.

Rothman and Walker have called the web 'an epidemiologist's dream come true'[3]. In their editorial they describe an Internet-based cohort study, to which participants are recruited electronically and followed by means of questionnaires posted over the Internet at specified intervals. Their sentiments are echoed in a number of other publications which explore the potential of the Internet for such studies and describe how recent software developments can be used to enhance data security, allow automated data compilation and evaluate in-coming data in real-time[4,5]. In fact, Internet-based epidemiologic studies are already being undertaken, as described by Kushi et al[6]. This study, funded by the Breast Cancer Research Program of the U.S. Army Medical Research & Materiel Command, solicits participation over the internet and uses electronic registration as a surrogate for a signed consent form. Data are collected by means of questionnaire modules and are encrypted during submission for protection of confidentiality. The Internet has also been proposed as a vehicle for facilitating the conduct of large multicenter clinical trials by allowing global access, fast interaction and automation[7]. Kelly and Oldham describe a prototype Internet Trials Service, hosted on a web server, which collects data, generates study numbers and performs automated randomization using Java applets. They describe mechanisms to ensure confidentiality and to authenticate patients' identities.

Interestingly, although the idea of performing a clinical trial on the Internet has not been specifically addressed, these studies collectively describe all the methods and technologies with which an intervention among an Internet-assembled cohort could be implemented and evaluated.

The Internet, therefore, has considerable potential for recruiting participants and conducting a clinical trial of a safe compound such as glucosamine or chondroitin sulfate. Huge numbers of people use the Internet on a regular basis, including an estimated 6 million people aged over 50 years. Older individuals who use the Internet display similar habits on the Internet to younger users, yet may be more reliable in their responses. Also, the methods and technologies for such an undertaking have already been described in other settings.

On the other hand, the recruitment of participants into an Internet-based trial of an intervention represents a significant departure from an observational study. We are not aware of any such endeavors at the current time, and there are many important issues that need to be addressed before such a study could be undertaken. For example, advertising methods, response and participation rates, demographic factors, validity of responses, case ascertainment methods, compliance, and participant retention are all critical factors in the conduct on an Internet-based trial. Evaluation of these variables, and study of the feasibility and costs, are necessary in order to develop the capability to perform Internet-based clinical trials.

Privacy and Security Issues Arising From Use Of The Internet As A Vehicle For Recruitment And Conduct Of Clinical Studies

As the Web and Internet become a part of daily life for many people, data privacy issues become increasingly important. The GVU Survey (1997) offers some insights into the conditions under which users are willing to reveal demographic information. The condition under which most respondents (78%) indicated that they would be willing to provide their demographic information was 'if a statement was provided regarding how the information would be used'. This suggests that respondents are more concerned with their right to control demographic information than any compensation they might receive for revealing it. The other statement that more than half (59%) of the users agreed with was 'if a statement was provided regarding what information was being collected'. A proportion agreed with conditions that involved some form of compensation for providing their demographic information. Only 6% reported that they would not give a site demographic information under any conditions. Most strongly objected to the idea that information could be sold to companies. We anticipate that many individuals will be prepared to communicate the relatively benign information which will be requested as part of this study, however, this is one aspect that will be evaluated as part of this proposal.

Perhaps a more important issue is the potential for interception of information posted electronically, and interference with scripts and data stored on the server. Fortunately a number of security enhancements are built into modern browsers and networks. Firstly, information posted on forms can be electronically encrypted so that only the intended recipient can decode the data. This function is available on the latest Internet browsers. Secondly, all forms subsequent to the introductory questionnaire can be sent using the allocated identification number without information which directly identifies the participant. Files stored on servers can be protected by electronic 'firewalls' which restrict access to designated users. This system is widely used in the Boston University School of Medicine server. It is implemented by means of unique login names, passwords and by the unique IP address of the user's computer. Finally, participant data can be stored on a secure server, as proposed here, to which only designated individuals have access.

Osteoarthritis As A Public Health Problem

Osteoarthritis is a common age-related disorder which is present in more than 10% of the population aged over 65 years, and which causes a substantial burden of disability and economic cost in the elderly[8]. Its prevalence in the US is believed to exceed 60 million people, and the incidence of symptomatic[9] knee and hip

OA has been estimated at 200/100,000 person years[10]. It is responsible for some 68 million work loss days per year[11], and for 70% of all hip replacements at a cost of $3 billion, in the US annually[12].

Despite its frequency in the population, therapeutic options in osteoarthritis are limited [13]. Current treatment recommendations highlight analgesics especially acetaminophen. Non-steroidal anti-inflammatory drugs, widely used to treat osteoarthritis, have not been found to be superior to acetaminophen for relieving pain or disability. While acetaminophen and non-steroidal drugs have been shown to be more efficacious than placebo for remediation of symptoms in osteoarthritis, their efficacy is limited. Long term NSAID use is associated with a 10% risk of gastric or duodenal ulcer[14] and also poses high risks of kidney disease and even central nervous system symptoms. Acetaminophen may cause long term renal and possibly, hepatic adverse effects in patients who use this drug regularly at high dose which is the current recommended regimen for osteoarthritis. Other treatment modalities for OA include exercise and muscle strengthening, but data supporting the efficacy of these modalities are incomplete and compliance with exercise regimens over the long term is inadequate[15]. Joint replacement surgery is effective in alleviating joint pain, but is performed only after years of pain and disability and may not return patients to their premorbid state of function[16]. In short, new treatments for OA are badly needed, especially ones that have favorable toxicity profiles and/or might have the potential for affecting the long-term course of disease.

Glucosamine And Chondroitin Sulfate

The idea that administration of glucosamine or chondroitin sulfate might have therapeutic effects in treating osteoarthritis by providing substrate for reparative processes in cartilage has been around since at least the 1960s. These compounds occur naturally in the body and may be involved in the repair and maintenance of normal cartilage. They have been used for many years in veterinary medicine for the symptomatic relief of arthritis. Recently, health and nutrition stores, and numerous news shows and popular books have promoted the use of glucosamine and chondroitin sulfate for the treatment of arthritis. On the basis of anecdotal evidence, the products appear to be gaining popularity among consumers. Different formulations of glucosamine are available in nutrition stores and the products do not require Food and Drug Administration (FDA) approval.

While there has been continuing interest in these compounds, this appears to have been tempered by lack of a plausible mechanism to explain how they might achieve a therapeutic effect. In fact, recent laboratory studies have indicated that glucosamine is absorbed through the gastrointestinal tract[17] and then rapidly distributed throughout the body with selective uptake by articular cartilage[18,19] where it stimulates both GAG and proteoglycan synthesis[20,21,22]. The biologic fate of orally administered chondroitin sulfate is less clear, but some evidence exists to suggest that the compound may be absorbed following oral administration, possibly as a result of pinocytosis[23]. Chondroitin sulfate is able to cause an increase in RNA synthesis by chondrocytes[24] which appears to correlate with an increase in the production of proteoglycans and collagens[25,26,27,28]. In addition, there is evidence that chondroitin sulfate partially inhibits leukocyte elastase and may, therefore, reduce the degradation of cartilage collagen and proteoglycans which is prominent in the osteoarthritis process[29,30,31,32].

Glucosamine and chondroitin sulfate have been the subject of numerous clinical trials in Europe and Asia, all of which have all demonstrated favorable effects from these compounds[33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48]. Many of these trials were often of small size, and few achieved high scores using a validated quality assessment instrument (see preliminary results; p. 18). Their results suggest that orally administered glucosamine in combination with chondroitin sulfate may be effective in providing symptomatic relief in patients with arthritis with no demonstrable toxicity. In those trials, the responder rate ranged from 50 to 80 percent of patients receiving medication and 20 to 30 percent in the placebo groups. In comparative trials, the efficacy appeared similar to NSAIDs, and there was a trend indicating that the beneficial effects may

persist for a few weeks after cessation of therapy. Importantly, no toxicity was associated with the use of these compounds.

A recently completed clinical trial from North Carolina using the validated WOMAC assessment instrument for knee OA symptoms has also demonstrated a therapeutic effect associated with the oral administration of a GS/CS combination. This study, which employed an intent-to-treat approach has suggested the effect is modest (see table 1).

Table 1 Results from the North Carolina clinical trial of glucosamine hydrochloride & chondroitin sulfate in patients with knee OA

		N	Baseline	S.E.	Termination	S.E.
WOMAC pain subscale	placebo	39	195.0	13.9	152.0	19.6
	active	33	189.0	13.9	128.0	14.9
Global assmt. (patient)	placebo	39	49.4	3.4	36.1	4.5
	active	33	48.9	4.0	30.8	4.1

Given their excellent safety profile these compounds have potential utility in the management of this common public health problem even if they are of modest effectiveness. Nevertheless, it is clear that further studies including larger numbers of participants will be required before definitive conclusions can be reached. Power calculations derived from the North Carolina study, and those performed independently by NIAMS suggest that approximately 320 participants will be required for each arm of the study. Thus, over a thousand participants will need to be required. In a traditional clinical trial setting this will require the participation of many centers and will cost well over $1 million. Such a trial is currently the subject of an NIH RFP (NIH-NIAMS-98-02).

Safety Of Glucosamine And Chondroitin Preparations

Thousands of patients have received some form of glucosamine or chondroitin preparation worldwide. We are aware of no major adverse events or fatalities from taking any of these preparations. The more rigorous controlled clinical trials of oral glucosamine and chondroitin preparations published as manuscripts in peer-reviewed journals include 400 participants taking oral glucosamine or chondroitin sulfate[41,33,34,37,41,42,43]. These have shown minor or moderate adverse rates to be similar to those taking placebo, and substantially lower than those taking a non-steroidal anti-inflammatory drug. Reported adverse events have generally been gastro-intestinal in nature. The results of a recent double-blind placebo-controlled of glucosamine hydrochloride in 94 patients with knee OA also found similar identical rate (12%) of minor adverse symptoms in the glucosamine and placebo groups (John Houpt MD - personal communication)[49]. No major adverse events were noted. In addition there have been no reports of allergic reaction to these compounds occurring among those allergic to beef, shellfish or to sulfonamides.

Parenteral administration of polysulfated glycosaminoglycan preparations has been shown to affect prothrombin time and activated partial thromboplastin time in animal studies, probably through heparin-like effects[50,51]. In a 30-day study of a oral glucosamine hydrochloride / chondroitin sulfate combination among Beagle dogs, however, no effects on coagulation parameters were observed[52]. Minor decreases in hematocrit and platelet count were observed but these remained within normal reference ranges. No hematologic abnormalities have been reported in the human studies of these compounds. Nevertheless, we will exclude individuals taking anticoagulants from this study.

Implications Of The Characteristics Of nutriceutical Products For Design Of Clinical Trials

Given the frequency of the disease in the general population, a safe therapy of even modest efficacy would be a useful intervention. In fact, there are a number of potential OA therapies suggested by epidemiologic and clinical studies which are safe and whose efficacy may be modest, or may be slow in onset. These include micronutrients such as vitamin E[53], vitamin C[54], vitamin D[55], and folic acid and vitamin B_{12} [56] nutritional products such as avocado / soybean oil[57], as well glucosamine and chondroitin sulfate (discussed above, p. 14). All of the compounds merit further testing in the context of clinical trials, yet the large number of participants required for power to detect a modest but clinically important symptom difference between active and placebo treatment is considerable. For example, power calculations for the recently released RFP f r a study of the efficacy of glucosamine and glucosamine/ chondroitin sulfate in knee osteoarthritis (NIH-NIAMS-98-02) suggest that over 1000 participants will be required for a three-arm study. The logistics and cost of this size of study are potentially prohibitive. In the setting of traditional medical center-based clinical trials, these numbers limit not only the number of potential therapies which can be studied, but also the ability to test differing formulations and combinations. Therefore, simpler and cheaper ways of testing these products in the population are urgently required to make headway in this field of research.

One alternate strategy is to perform these studies using the Internet. This approach has many advantages in the study of non-toxic remedies for osteoarthritis. Firstly, with over 5 million estimated adult users in the US alone and continuing exponential growth, the Internet offers considerable potential for participant recruitment (24% of Internet users search for information daily), and facilitates communication over large geographic distances. Secondly, the lack of toxicity of these products minimizes the need for physician contact with participants. Thirdly, disease definition is less complex for osteoarthritis than for other rheumatic diseases. Fourthly, validated questionnaires which use self-reported information and which can be administered over the Internet, are available for evaluating pain and disability in individuals with osteoarthritis of the knee and/or hip.

Measuring Change In Osteoarthritis: the WOMAC Osteoarthritis Index

The WOMAC is a tridimensional disease-specific self-administered health status questionnaire[58,59]. It probes clinically important, patient relevant symptoms in the areas of pain, stiffness and physical function in patients with OA of the hip or knee[60]. The index consists of 24 questions (5 pain, 2 stiffness, 17 physical function) which can be completed by the patient in 5 minutes. WOMAC has high test retest reliability for all scales, and validation studies have showed high correlations with other indices probing the same dimensions including MHIQ, Doyle, the Lequesne index and others[58,61]. Responsiveness has been tested in non-steroidal trials and each aggregated subscale score (e.g. pain) has been found to detect the effect of NSAID's[62], and to detect a clinically important statistically significant difference in efficacy between two NSAIDs[63].In terms of sensitivity to change, WOMAC has been compared to other measures of patient status in OA including HAQ, AIMS, the Doyle index the Lequesne index and measures of walk time, range of motion, and has generally been found to be more sensitive to change (relative efficiency compared to other instruments ≥1) [62,63,64]. It can be utilized in a site-specific fashion and has been shown to discriminate between outcomes in opposite joints in the same patients[65]. The WOMAC has been recommended as a measure for assessing 'slow-acting' drugs in OA, and has been employed in two recently completed clinical trials of glucosamine and chondroitin for knee OA (personal communications from Das MD, and from Joseph Houpt MD, Dept. of Rheumatology, University of Toronto). In addition, a computerized version of the WOMAC, completed by participants directly on a computer screen, has recently been validated[66]. We will, therefore, test the use of the pain subscale of the WOMAC as an outcome measure in the model clinical trial.

C. Preliminary Studies

Development Of Prototype Web Site

We have constructed a prototype of the web pages to be used in this study and have posted them within the Boston University Medical School Website. These pages represent a demonstration of the study concept and are being continually developed. Although preliminary, they are already capable of providing information, obtaining consent and collecting preliminary data onto an ASCI file database. They can be accessed through the medical school's homepage (http://www.bumc.bu.edu/ - follow link under 'Projects' to 'Arthritis Clinical Research'), or can be reached directly[68]. The pages provide information about the study, and invite participation. One of the pages is a consent form presented in a 'question and answer' fashion, which can be printed, signed, and sent by mail to the study coordinator. Individuals who wish to determine their eligibility for the study are taken by a 'link' to a form which is currently posted on a restricted-access desktop computer located in the office of the Primary Investigator. The form asks questions about knee pain, osteoarthritis diagnosis, availability of knee radiographs, and use of analgesic medication. It also asks for demographic information and an Email address. Information entered into the form fields and submitted is added to cumulatively to an ASCI file database located on the hard disk of that computer. The name of the computer submitting the information, and its IP address, are also obtained and saved in this database. Further refinements which will be incorporated into these pages include automation of data collection, real-time monitoring of data quality (error checking), generation of automated responses by Email and construction of Java applet devices to represent visual analog scales for the WOMAC questionnaires.

D velopment of a screening questionnaire for symptomatic knee osteoarthritis

The aim of this study was to develop and validate a questionnaire with which to screen for knee OA. We created a 28-item survey containing randomly ordered questions about aspects of knee OA symptoms, and mailed it to subjects in the Framingham Osteoarthritis Study. Radiographs and a knee pain question from earlier exams were used to characterize subjects as cases. We used recursive partitioning methods to test the performance of questions used independently and in combinations. 1939 subjects (mean age 61 yrs, 56% women) responded to the mailing among whom 210 (10.8%) had symptomatic knee OA. The two most efficient screening strategies consisted of single questions: (1) During the last month, did you have any knee pain or discomfort when walking 2 - 3 blocks (1/4 mile)? [sensitivity=0.67, specificity=0.89, positive predictive value=0.37] (2) Has a doctor ever told you that you have osteoarthritis in your knees? [sensitivity=0.62, specificity=0.89, positive predictive value=0.35]. Using questions in combination did not improve their efficiency. We conclude that these questions perform best in screening for knee OA but require an x-ray to confirm case status. This work was presented at the Annual Meeting of The American College of Rheumatology (see appendix)[67].

Experience With Ascertainment Of Geographically Remote Cases: Factors Associated With Systemic Lupus Erythematosus Among Participants In The Black Women's Health Study

This is an epidemiologic study on which Timothy McAlindon MD is the Primary Investigator, funded through The Boston University Arthritis Center Multipurpose Arthritis And Musculoskeletal Diseases Center grant (R01 AR20613). Funding commenced in September 1997. The overall goal of this project is to study risk factors for SLE in the largest cohort study of Black women ever assembled, the Black Women's Health Study (BWHS).

SLE cases among the BWHS participants are identified using a stepped screening strategy. The first step will consists of a validated 10-item lupus screening questionnaire (LSQ), which was included in the 1997 survey of the entire cohort. All participants who screen positive on the LSQ and who report physician-

diagnosed lupus receive a letter asking them for permission to write for copies of relevant portions of their medical records. They are also asked to provide names of hospital and physicians where records will be available. On receiving signed consent, we send letters to the cited hospitals/physicians asking for these copies. The letter used for the hospital request gives examples of laboratory tests and text content which is informative for our purposes. The letter to the physician simply includes a 'checklist' of American College of Rheumatology (ACR) criteria for the classification of SLE. Two rheumatologists then independently perform chart abstraction to document presence of each of the ACR criteria for the classification of SLE

This study is proceeding according to the projected timeline. So far, 51,979 / 64,570 [80.5%] participants have responded to the 1997 mailing to the overall cohort, among whom 531 screened positive on the LSQ and reported a physician diagnosis of SLE. After one completed mailing, we have received consent from 278 (52.3%) of these women, with only 2 refusals. We have requested copies of medical records and a physician ACR checklist for 259 participants and have received copies of records for 157 (61%) and a physician checklist for 131 (51%). Chart abstraction for ACR criteria for SLE is now in progress.

A Meta-Analysis And Quality Assessment Of Clinical Trials Of Glucosamine And Chondroitin Treatment For Osteoarthritis Of The Knee Or Hip

We, performed a meta-analysis and quality assessment of clinical trials to both evaluate the likely efficacy of the compounds, and the quality of the evidence (accepted for presentation at the 1998 ACR meeting - see appendix). Studies eligible for inclusion were double-blind placebo-controlled trials of 4 weeks or greater duration, testing oral or parenteral glucosamine or chondroitin for knee or hip OA. These trials were required at a minimum to report p values and size of treatment effect. We sought studies using MEDLINE, manual searches of manuscripts and journal supplements, and by contacting authors of published manuscripts and content experts. Two observers independently scored study quality using a validated inventory. We computed the probability that the observed number of positive studies might have occurred by chance if the treatments were in fact ineffective using the sign test, and the number of negative studies which would be required to mak this result null ($p \approx 0.5$). Thirteen trials met our eligibility criteria. Quality scores were substantially lower for abstracts compared with manuscripts. Major deficiencies related to descriptions of randomization, blinding, and completion rates. All studies were classified as positive, and demonstrated large effects with a mean score reduction compared to placebo of 39.5% (s.d. 21.9) for glucosamine, and 40.2% (s.d. 6.4) for chondroitin. The probabilities for this outcome in the absence of any true effect are $p=0.016$ for glucosamine, and $p=0.008$ for chondroitin.

Thus, clinical trials of glucosamine and chondroitin show substantial benefits in the treatment of OA, but provide insufficient information about study design and conduct to allow definitive evaluation. We conclude that further studies are needed to test the efficacy of glucosamine and chondroitin. The results of this meta-analysis have been

D. Experimental Design and Methods

The overall objective of this study is to evaluate aspects of the feasibility, utility and validity of performing a clinical trial using the Internet. We will address these aims by enrolling 100 people into a *model* Internet-based trial. This will be a 14-week double-blind trial of glucosamine hydrochloride 500mgs / chondroitin sulfate 400 mgs combination three times/day in the treatment of symptoms due to knee osteoarthritis. Please note that we are concerned with evaluating the *processes* involved with the performance of the study, and not with the effectiveness or otherwise of these compounds. An overview of the study process is represented in the Appendix, Figure 1.

We will evaluate the study outcomes by (i) comparing the response rates and costs of the four different advertisement strategies (ii) describing the numbers and demographic characteristics of respondents, and the

subset who actually participate (iii) documenting compliance with the study protocol (iv) comparing pain scores, and change in scores, and their standard deviations, with those found in traditional settings. (v) Finally, using these data, we will estimate the cost of performing a fully powered clinical trial of these compounds over the Internet, and compare this figure with that required to perform such a trial in a traditional clinical setting.

1 Architecture Of The Study Web Site

An overview of the study web site is presented in the Appendix, Figure 1. The study Website is situated on the Boston University School of Medicine server and is linked with the homepages for the Department of Medicine and the Rheumatology Section. This is a secure server. A prototype of the site can be visited through the medical school's homepage (http://www.bumc.bu.edu/ - follow link under 'Projects' to 'Arthritis Clinical Research'), or can be reached directly[a]. The study homepage includes a solicitation for participants. It is linked to subsidiary pages which describe the study and lead to an eligibility screening page and a consent form (which can be printed, signed, and sent by mail to the study coordinator). The eligibility screening page asks about knee pain, osteoarthritis diagnosis, availability of knee radiographs, and use of analgesic medication. It also requests demographic information and an Email address. Information entered into the form fields and submitted is added cumulatively to an ASCI file database, along with the name of the computer submitting the information and its IP address.

To evaluate symptom severity, we will construct an Evaluation Page that will include the WOMAC questions, and a global pain severity scale. We will use Java applets to simulate visual analog scales. Although these actually function as ordinal scales, by means of multiple small increments, they have been previously used to good effect in Internet-based questionnaires (personal communication, Leslie Lenert MD, UCSF). Participants will need to enter their login name and password to access the evaluative page. They will be prompted to fill out the evaluative page at the requisite timepoints by means of Email messages. The data submitted from this page will be collected into a separate ASCI database. This will interface with a Microsoft Access program to facilitate data monitoring and analysis. The Evaluation Page will include a request for each participant to provide a count of residual capsules in the bottle.

Further refinements which will be incorporated into these pages include automation of data collection, real-time monitoring of data quality (error checking), generation of automated Email responses and reminders, and construction of Java applet devices to represent visual analog scales for the WOMAC questionnaires.

2 Testing ways of publicizing Internet-based studies

Recruitment will take place using the Internet. To achieve this we will first create a web page dedicated to this study. This page will provide general information about knee and hip osteoarthritis and guidelines for their management. It will provide links to pages with further education resources. It will provide basic information about the study, and solicit participation.

We will publicize the study web site using a variety of Internet-based and traditional strategies:

(i) Internet-based, health-related [e.g. advertisements, links, on Arthritis Foundation web site]
(ii) Internet-based, non-health related [e.g. advertisements, links, on other web sites]
(iii) non-Internet, health-related [e.g. advertisement in Arthritis Foundation newsletter]
(iv) non-Internet, non-health related [e.g. advertisement in Internet magazine].

So that we can measure the response rate from each of these four strategies separately, we will construct four separate web pages to act as gateways to the home page. Each gateway web page will include a counter to record the number of 'hits', and will record IP addresses so that we can determine the route through which each participant arrived at the homepage. (Participants who did not access the site thr ugh one of these

gateways will be classified as having found the study independently of our advertising strategies). W will compare the yield of each of the four advertising strategies. We will determine the positive predictive values for documented knee OA according to the origin of the response, and basic demographic characteristics (age, gender) of each applicant.

3 Preliminary screening of individuals expressing interest in participating in the study

The study homepage will direct individuals who are interested in participating in the study to a knee OA screening questionnaire (the Preliminary Eligibility Screen). This will ask

- "During the last month, did you have any pain or discomfort when walking 2-3 blocks (¼ mile)?"
- Have you ever been diagnosed by a physician as having of osteoarthritis of the knee ?
- if they have ever had a knee radiograph demonstrating evidence of knee OA
- if they take medications regularly for their knee pain
- the questions from the pain subscale of the WOMAC questionnaire
- for demographic variables including age, gender, ethnicity, occupational level, comorbidities and comedications

We have previously validated the first two questions as first steps in a screening algorithm for the classification of knee osteoarthritis (see p. 19). Respondents will submit answers to these questions using the electronic form on the eligibility screening page, and will receive a response from the study Website indicating whether or not they have passed this preliminary eligibility screen. Those who have passed the preliminary eligibility screen will be directed to the consent form page. Ineligible individuals will be provided with information about further resources from whom information and counseling may be available (e.g. Arthritis Foundation).

4 Authenticating The Identity of Respondents

One of the major concerns in soliciting participation over the Internet relates to the identity of the individual transmitting information. Although it seems unlikely that a person would assume another individual's identity in order to enter into a trial of a 'nutriceutical' (and we will not be offering reimbursement), the authenticity of the respondent's identity is of importance for reasons of confidentiality, and in order to obtain informed consent. Therefore, we will take steps to determine, as far as possible, that the identity of the respondent is valid, and that he or she is aged over 21 years. We will inform all potential participants about the steps which will be taken before they submit any information to us.

As a first step, we will ask individuals who are interested in participating in the study to submit their name, date of birth, address, telephone number(s), and email address (this occurs on the preliminary eligibility page). We will ask them to confirm that they are the sole user of this Email address. This is equivalent to the level of inquiry undertaken in traditional clinical trials settings, except that we will not have face-to-face contact. Provision of this information will serve as a demonstration of interest in the study. Respondents who pass the preliminary eligibility screen will be sent a unique login name and password by mail. These measures will serve as a first step in reducing frivolous responses. In the consent form we will ask respondents to confirm their identity and will emphasize the legal nature of the document. We will also ask them for permission to write to their physician and/or hospital to (i) obtain a knee radiograph or a copy of a knee radiography report (ii) ask their physician to complete a short knee OA diagnosis checklist. Thus, corroboration of the respondents' identities will also occur as a by-product of the process of validation of their knee OA status.

One further step will be taken during the course of enrollment and determination of eligibility to validate the identity of the respondent. This will occur before any individual is provided with the study compound and will take the form of a telephone conversation between the study administrator and the respondent. The

respondent will be informed that the objective of the call is to verify that they are indeed the individual who expressed interest in the study over the Internet, and that they have continued interest in participation. They will be asked to confirm that these assertions are correct.

Traditional clinical trials do not routinely require confirmation of identity, or request social security numbers unless payments are to be made. Potential recruits are often respondents to advertisements and frequently are unknown at the institution running the trial. Therefore, the potential to provide an invalid identity exists even in the conventional clinical setting. In our study, although Internet-based, we propose to explore measures to corroborate the identity of the respondent, which we feel are at least as rigorous as those employed in traditional clinical trials. In addition, the potential for frivolous or even malicious responses is further reduced by the facts that (i) no remuneration will be provided to participants, and (ii) the investigative compound is of little interest to individuals in general other than those with OA. Also, the potential for harm is slight because the nature of the information requested from respondents is relatively benign (data relating to knee OA diagnosis and symptoms) and because the investigative compound is non-toxic.

5 Obtaining Informed Consent

We will ask individuals who express a desire to participate in the study to print out a hard copy of the consent form. (Individuals who do not have printing capability will be able to request a consent form to be sent to them by mail.) The consent form will include a detailed description of the study. It will also ask them for permission to write to their physician and/or hospital (i) to obtain a knee radiograph or a copy of a knee radiography report (ii) to ask their physician to complete a short knee OA diagnosis checklist. It will ask respondents to confirm their identity and will emphasize the legal nature of the document. They will be asked to sign this in the presence of a witness, and to mail it directly to the study coordinator. Determination of eligibility and further data collection will not proceed until a we receive a signed consent form.

6 Documenting Knee Osteoarthritis

Participants will be required have symptomatic radiographic osteoarthritis of one or both knee joints. We will classify knee OA according to the ACR criteria for the classification of knee OA(ref) using (i) the response to the question "During the last month, did you have any pain or discomfort when walking 2-3 blocks (¼ mile)?", and (ii) radiographic appearances. Our classification system is contingent on respondents having had previous radiography of their knees. We will seek radiographs, copies of radiographs, or copies of the radiographic report. We will do this by writing to the institution and/or physician cited by the respondent as having performed the radiography. We will not ask respondents to have radiographs taken, however. Thus, individuals who have never had radiography of their knees will be ineligible for the study. Radiographs will be scored for tibiofemoral osteoarthritis using the Kellgren and Lawrence (K&L) grading system. A knee will be considered to have OA if the radiograph shows at least grade II changes (i.e. at least one osteophyte). When only a radiographic report is available, we will evaluate this for mention of tibiofemoral osteophytosis. If present, this knee will be considered to have a K&L score of at least grade II. Individuals will thus be classified as having knee OA if they answer in the affirmative to the knee pain question, and have radiographs demonstrating OA changes of at least Kellgren and Lawrence grade II (or equivalent on a radiographic report). As such, these individuals will fulfill the clinical algorithm according to the ACR classification criteria for knee OA (see table 2).

- knee pain
- at least one of the following:
  a) Age ≥ 50 years
  a) Stiffness < 30 mins
  a) Crepitus
- osteophytes

Table 2 ACR Clinical and Radiological Criteria for Classification of Idiopathic OA of the Knee (91% sensitive; 86% specific)

In parallel with obtaining documentation of knee OA by means of radiographs or their reports, we will send a short diagnostic checklist to each participant's physician (see appendix). This will ask for information documenting OA diagnosis and medication use (including other experimental compounds). The objective of utilizing parallel approaches is to determine the optimal mode of case validation for Internet-based studies. We have used the physician checklist approach in the study of Factors Associated With SLE Among Participants In The Black Women's Health Study, where it appears to have great utility (see Preliminary Results section, p. 20).

7 Determining Eligibility For The Clinical Trial

This study is concerned with aspects of the feasibility, utility and validity of performing a clinical trial using the Internet. It is *not* our aim here to determine the *efficacy* of chondroitin/glucosamine, but we do intend to replicate aspects of such a study in order to determine how best to perform a future Internet-based trial. Therefore, we will impose inclusion and exclusion criteria (tables 3 & 4), and (since the possibility of receiving a placebo may deter some potential participants) we will randomize participants to receive the 'active' compound or a placebo in a double-blind fashion.

Individuals eligible for this study will be men and women aged over 50 years with symptomatic knee OA fulfilling the clinicoradiologic ACR criteria for the classification of knee OA (see Table 2) and consuming analgesic medication *on most days*. We will determine the presence or absence of contributory features by asking standard validated knee symptom questions over the Internet, and by obtaining documentation of radiographic osteoarthritic changes by obtaining the original radiographs, or formal radiological reports. Participants will be required to have undergone the measures intended to verify their identity, and to have provided written consent, including provision of addresses through which radiographs or their reports may be obtained.

Table 3 Inclusion Criteria

1. At least one knee meeting clinico-radiologic ACR Criteria for Knee OA determined by
   a) knee pain, defined as affirmative response to the standard question 'During the last month, did you have any knee pain or discomfort when walking 2 - 3 blocks (1/4 mile)?'
   b) age ≥50 years
   c) at least one area of tibiofemoral or patellofemoral osteophytosis seen on a radiograph or documented in a formal radiology report
2. WOMAC pain subscale score (range 0-20) of > 2
3. Use analgesics for knee OA *on most days*
4. Willing to give written informed consent after an explanation of the study

Table 4 Exclusion Criteria

1. Individuals taking anticoagulants
2. Individuals taking medications with potential MMP-inhibitory properties (e.g. tetracyclines or structurally related compounds)
3. Individuals who received intraarticular injections in a knee joint within 60 days of Encounter 2
4. Individuals taking other agents claiming to possess disease/structure-modifying properties (e.g. avocado/soybean oil or glucosamine and/or chondroitin sulfate containing compounds)

8 Enhancing The Characteristics Of The Sample To Include M tivated Participants: The Run-In Phas

We will send all eligible participants a unique login name and password so that they can access the Evaluation Page. We will include an on-paper pill diary so that they can keep a record of analgesic use during the observation period. The evaluation page collects data about symptoms and medication use and weight at each 'virtual encounter'. We will ask enrollees to access the page and conduct Encounter 1, which is the start of the 2-week run-in phase of the trial. We will instruct participants to keep a record of their daily analgesic use on the paper pill diary, and to revisit the Evaluation Page exactly 2 weeks following Encounter 1. During this period they will be encouraged to contact us, by Email or telephone, with any issues or questions that arise. We will provide a toll-free number to enable them to call us directly. Encounter 2 represents the beginning of the treatment period. We will, however, make provision of the study pills contingent on full and adequate completion of the Evaluation Page at both Encounter 1 and Encounter 2. This includes provision of analgesic use data during the run-in phase, transcribed from the paper pill diary. The objectives of the run-in phase are to (i) serve as a familiarization and trouble-shooting exercise for participants in respect of data provision (ii) allow selection of participants who are likely to remain compliant with the protocol into the treatment phase of the study (iii) establish baseline values for outcome measures.

9 Provision Of Study Capsules To Participants

The study capsules will be provided by Nutramax Laboratories, Inc.. 'Active' and placebo pills will be indistinguishable and will only be identifiable by a code number present on the label. The Boston Medical Center Pharmacy (which is open 24 hours /day) will store the capsules, perform randomization, and break codes where necessary. Participants who adequately complete the run-in phase of the study will be randomized to receive 'active' treatment or placebo. The results of the randomization will be not be provided to the investigators or participants. The 'active' pills will contain a combination of glucosamine hydrochloride 500mgs and chondroitin sulfate 400 mgs. The capsules also contain 66 mgs of ascorbate as a preservative. Participants will be asked to commence the study pills on receipt, two each morning and one each evening. Obviously, there will be a few days delay between Encounter 2 and commencement of the study pills.

10 The Clinical Trial

Participants will be asked to take three capsules per day for 12 weeks (two each morning and one each evening). They will be asked to maintain use of the same type of analgesic during this period, although the frequency and dose may be altered as required. During this period they will keep a daily record of analgesic consumption and report any adverse events. They will provide responses to the pain assessment questions every two weeks by logging into the Evaluation Page. We will send them Email reminders shortly prior to each anticipated encounter to enhance compliance.

11 Outcome Measures And Use Of Questionnaires For Reporting Responses

The primary outcome assessments for the clinical trial will be (i) the WOMAC (ii) global pain visual analog scores (iii) use of analgesics. These measures will be collected using the Evaluation Page and stored cumulatively in a database. Please note that while these measures are included as part of an evaluation of the processes involved in performing a clinical trial using the Internet, and not to determine the *effectiveness* of glucosamine/ chondroitin sulfate.

12 Measures To Enhance Continuing Participation And Compliance

We will implement a number of measures which have been found in traditional studies to enhance compliance with the study protocol. These will included establishing phone contact with each participant,

regular Emailed reminders and updates, establishment of an open channel of communication between participants and the study coordinator using Email and a toll-free telephone number. In addition we will offer minor incentives for continuing participation, such as study keychains and mugs, and magazine subscriptions. While being of little financial value, these measures have been found to increase participants' sense of connection with longitudinal studies.

13 Handling Of Adverse Events

Glucosamine and chondroitin are classified as food supplements and are non-toxic. No serious adverse events have ever been reported for any participant in a study of these compounds, and reported side-effects of minor severity have occurred with equal frequency among those taking active compound compared to those taking placebo. Also, no allergies have been reported from oral consumption of these products. Despite this, there remains a small possibility of unforeseen adverse reactions. Therefore, we will incorporate measures to monitor reported adverse events. Participants will have the opportunity to report any perceived adverse events on their pill diary form. In addition, for events perceived by the participant to be of greater than minor severity, we will provide a toll-free number through which they may contact the study administrator or the P.I. Randomization codes will be kept at the Boston Medical Center Pharmacy which is open 24 hours/ day.

14 Confidentiality And Security Of Information Provided By Participants Over The Internet

We will go to considerable lengths to ensure security of participants' data. Firstly we will issue each participant a unique username and password to enable them to log into their personal study forms. The only other personnel with access to these forms will be the PI and the Website data manager. This measure will prevent other individuals from accessing, or tampering with, a participants' information. Next, by offering software adaptations if necessary, we will facilitate encryption of data transmitted by each participant (data encryption is a function now provided routinely with current web browsers). This will ensure that all data are transmitted in a form which is interpretable only to the study web site. Thirdly, we will store all received data on a secure server within the Boston University School of Medicine network. This network has high levels of internal security with the ability to impose different levels of access to different sites based on an individual's access password. Using this system, we will confine access to study data to the P.I. and the Website systems administrator. Finally we will assure all participants that any data provided will be for the sole use of research study, and will not be shared with any other party.

15 Data Analysis And Statistical Considerations

The primary goals of this study relate to testing aspects of the feasibility, utility and validity of performing a randomized controlled clinical trial using the Internet. Specifically, we will evaluate the study outcomes by (i) comparing the response rates and costs of the four different advertisement strategies (ii) describing the numbers and demographic characteristics of respondents, and the subset who actually participate (iii) documenting compliance with the study protocol (iv) comparing pain scores, and change in scores, and their standard deviations, with those found in traditional settings. (v) Finally, using these data, we will estimate the cost of performing a fully powered clinical trial of these compounds over the Internet, and compare this figure with that required to perform such a trial in a traditional clinical setting.

(i) We will compare the utilities of the different study advertisement strategies

This analytic step relates to determining the most efficient way of soliciting participants over the Internet. Our utility parameters for each of the advertisement strategies will consist of (a) the response rate in terms of the yield of valid participants, and (b) the cost of recruiting each participant. These parameters will be determined from data collected from the 4 'gateway' Web pages (one for each of the 'advertising' strategies). Each of these pages will log the IP address of each browser's computer. This will enable us to determine the route through which most participants arrived at our site. Some participants may find the site independently,

and will not be 'logged' at any of the 'gateway' pages. These individuals will be classified as independent arrivals. W will determine the number of participants derived though each of these (five) routes. We will determine the proportion of those screened who are subsequently found to be eligible according to their route of arrival at our Web site (positive predictive value). Finally, based on advertising costs, we will calculate the cost per participant for each of the four advertising strategies. These statistics will enable us to rank the utility of the various recruitment strategies.

(ii) We will describe the numbers and demographic characteristics of respondents and participants
We will provide simple descriptive statistics of those undergoing eligibility screening and those who finally participate. These will include distributions of age, gender, ethnicity, occupational level from the Preliminary Eligibility Form, and self-reported weight (on the Evaluation Form). We will compare these distributions with those reported in traditional clinical trials of these and other osteoarthritis-related compounds.

(iii) Documenting Compliance With The Study Protocol
We will ask participants to keep a daily record of consumption of study capsules as well as all concomitant analgesics or non-steroidal anti-inflammatory analgesics. They will be requested to enter these data into fields on the Evaluation Page. This will function as an indicator of compliance with the study medication as well as a measure of analgesic requirements. Also, we will evaluate adherence to the study protocol for each participant by reporting (i) the proportion of all questions which were adequately completed during the course of the study and (ii) the proportion of participants who persevered until the end of the study (completion rate).

(iv) Performance Of Symptom Evaluation Instruments Of The Internet
We will describe the distribution of each of the symptom assessment questions administered on the Evaluation Page. This will include the global pain visual analog scale, the overall WOMAC scores, and the score of each WOMAC question item. We will compare these values to those obtained during the validation studies of this instrument[58,61], and from traditional clinical studies of glucosamine (Data obtained through personal communication with John Houpt MD[69]).

(v) Estimating The Cost Of An Internet-Based Clinical Trial
We will estimate the cost of performing a fully powered clinical trial of nutritional products over the Internet. To do this, we will extrapolate from the item costs involved in performing the proposed study, including utilization of the most efficient advertising strategy. We will build in the personnel, software and hardware costs. We will assume that a fully powered study will require approximately 320 completers per arm, as suggested in the recent RFP (NIH-NIAMS-98-02) and adjust for the drop-out and non-compliance rates found in our study in the our number projections. We will perform sensitivity analyses to accommodate variations in study design, such as multi-arm or factorial design approaches. We will compare the range of costs with those required to perform similar studies in a traditional clinical setting.

16 Timeline

1999	2000	2001	2002
1.			
2.			
3.			

1. Development and testing of the Website and its functions
2. Advertising, recruitment and conduct of the model Internet-based clinical trial
3. Data processing, cleaning & analysis; presentation of findings; manuscript preparation

E. Significance

The explosive growth in Internet use is one of the more remarkable phenomena of the last decade. With 52 million users in the US, and many more across the globe, the Internet is the single most effective modality for reaching large numbers of people. Recent advances in software technology have made the Internet easy to use, and allow construction of interactive web pages through which information can be collected and assimilated into databases. These attributes make the Internet an extraordinarily powerful resource for performing questionnaire-based research. Perhaps one of the most enticing medical applications of the Internet, however, is the possibility of revolutionizing certain forms of large trial design by performing these on-line at relatively little expense compared to traditional settings. While on-line surveys are now commonplace, this application has received little attention, possibly because clinical investigators encounter an unfamiliar set of issues in trial design and conduct. The Internet probably has its greatest utility for clinical trials in a setting where (i) a safe compound is hypothesized to be effective in the treatment of (ii) a disorder whose severity can be assessed using self-reported questionnaires, and (iii) where large numbers of participants are required to demonstrate effectiveness.

This situation is now present for knee osteoarthritis (OA), a major public health problem which imposes a considerable burden of pain, disability and expense among the elderly population. There are currently no proven effective medical remedies for this disorder, yet a number of nutritional compounds may be modestly effective. As such, these therapies could prove to be valuable therapies because of their lack of toxicity, and two of them are the subject of a recent NIH RFP. A considerable obstacle, however, is that the detection of modest effectiveness in a traditional clinical trial requires hundreds of participants and costs millions of dollars. These constraints are likely to prove prohibitive in respect of testing all promising compounds and determining their optimal mode of utilization. Thus, many valuable agents may never be adequately evaluated in traditional clinical trial settings.

The overall objective of this study is to test the feasibility, utility and validity of performing a clinical trial using the Internet. The longterm objective is to develop the capability to develop and test potential public health interventions for rheumatic diseases among large samples by exploiting the huge potential offered by the Internet.

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G. Co-Investigators

Doreen Nicastro BS MPH is Director of Training and Communications at The Office of Information Technology, Boston University School of Medicine (BUSM). She is responsible for directing the implementation of a new strategic plan at BUSM to expand the information infrastructure of the campus by working with Departments, Projects and Centers in creating online databases and websites over the campus intranet. Her skills and insight into the planning and development of an interactive website nested within the BUSM online databases are critical to the success of this project.

EXHIBIT A - PAGE 40

From: nicastro@bu.edu <nicastro@bu.edu>
To: tmcalind@bu.edu <tmcalind@bu.edu>
Cc: OITDirectors@bumc.bu.edu <OITDirectors@bumc.bu.edu>
Dat : Monday, August 31, 1998 5:21 PM
Subject: RE: Clinical Trials Over the Internet

To Whom It May Concern:
I am writing on behalf of Dr. McAlindon and the Clinical Trials Over the Internet proposal. I am the Director of Training and Communications in the Office of Information Technology at Boston University Medical Campus. I have been involved in the Internet and Web development for the past five years. Boston University School of Medicine was the first medical school on the web. The site was administered and supervised under my direction.

Over the past few years, organizations have begun to realize the potential of the web as a communication, education and research tool. By using Internet standards, organizations are able to create web sites to administer projects such as online course registration, courses information, tel-medicine and research. Boston University School of Medicine is committed to this important project and the Office of Information Technology will provide much of the information technology infrastructure to support this exciting endeavor. We look forward to working with Dr. McAlindon and the Arthritis Center on this important and progressive research project.